

## Uncomfortable Uncertainty: Do OTC Analgesics Disrupt Fetal Germ Cell Development?

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Women use over-the-counter analgesics for a number of reasons during pregnancy: headache, fever, joint pain, or injury.<sup>1</sup> However, a growing number of epidemiological and experimental studies suggest that nonprescription pain relievers taken during pregnancy may interfere with the action of key hormones that affect fetal genital development, says Rod Mitchell, a pediatric endocrinologist at the University of Edinburgh in the United Kingdom and senior author of a new report in *Environmental Health Perspectives*.<sup>2</sup>

In the new article, Mitchell and colleagues show that exposure to both acetaminophen and ibuprofen adversely affected germ cell development in rodent and human fetal gonadal tissue. The U.S. Food and Drug Administration considers acetaminophen the safest analgesic to take throughout pregnancy when used as recommended.<sup>3</sup> Ibuprofen is typically not recommended for use in the first and third trimester due to an increased risk of certain birth defects.<sup>4</sup>

The team, led by University of Edinburgh PhD student Pablo Hurtado-Gonzalez—now a postdoctoral fellow at the University of

California, Los Angeles—obtained human fetal testis and ovarian tissue from pregnancies terminated during the first or second trimester. They grew the tissue pieces in culture, exposing them to either ibuprofen or acetaminophen at levels consistent with human therapeutic doses. The cultured tissue was exposed for up to seven days.

The researchers assessed the effect of treatments by counting gonocytes within the tissue samples. Gonocytes are the germ cells that eventually become sperm and eggs. They found that, in comparison with unexposed testis tissue, acetaminophen- and ibuprofen-treated tissue had an average 28% and 22% fewer gonocytes, respectively. In the ovarian tissue, they saw a 43% reduction in gonocyte number in acetaminophen-treated tissue, and ibuprofen exposure reduced gonocytes by 49%.

During pregnancy, women typically use analgesics for short periods, so the researchers wanted to test whether a shorter-term exposure also could induce changes in gonocyte number. After grafting second-trimester human testis tissue into mice, they found that grafts from mice dosed with acetaminophen had



Reproductive health scientist Shanna Swan says it may be prudent for pregnant women to skip over-the-counter pain relievers unless they have a serious medical condition, such as high fever, severe pain, or migraine headaches. They should always ask their doctor before taking any medicine. Image: © LaraBelova/iStock.

17% fewer gonocytes after 24 hours than grafts from untreated mice.

Previous studies have suggested that acetaminophen may have antiandrogenic effects in the fetal environment.<sup>4,5</sup> Treatment of pregnant mice has been reported to cause genital abnormalities in male offspring.<sup>6</sup> Findings from human observational studies suggest that maternal exposure during pregnancy may increase the risk of undescended testicles (cryptorchidism) and reduce the distance between the anus and the base of the penis, a measure known as anogenital distance, in boys.<sup>6</sup>

However, during gestation, germ cells do not express androgen receptors, says Mitchell. The researchers therefore wanted to test which other molecular pathways might be responsible for the reduction in gonocyte number that they observed.

Mild analgesics, including acetaminophen and ibuprofen, are known to target the prostaglandin pathway.<sup>7</sup> Prostaglandins are biologically active lipids that play many important roles in the body, from promoting the immune system's inflammatory response to initiating male genital development *in utero*.<sup>8</sup>

A previous study found that maternal exposure to indomethacin, an analgesic with a similar mechanism of action to ibuprofen, blocked prostaglandin signaling in fetal rat testicular tissue.<sup>9</sup> Similarly, in a recent article, Mitchell and colleagues reported that exposing pregnant rats to indomethacin or acetaminophen blocked prostaglandin signaling in fetal ovarian tissue.<sup>10</sup> In the present study, they showed that blocking prostaglandin E<sub>2</sub> signaling in human germ cells mimicked the effects of acetaminophen and ibuprofen in the same cell line.

The findings support previous studies showing that acetaminophen exposure can affect both male and female gonadal development, says David Kristensen, a biomedical scientist at the University of Copenhagen in Denmark. The most concerning finding may be the effect on cultured human ovarian tissue, says Kristensen, who was not involved in the research. "What we now really need are the epidemiological studies to further [assess] the risk of female reproductive problems after prenatal analgesic exposure," he adds.

Females are believed to be born with all the eggs they will ever have, so any loss of gonocytes in the prenatal period could have long-term consequences for egg reserves and reproductive lifespan. Previous research in rodents linked analgesic exposure during pregnancy to a reduction in ovarian follicles and reduced fertility.<sup>10</sup>

For males, on the other hand, there is some evidence—at least in rodent models—that sperm cell precursors may continue to proliferate after birth.<sup>10</sup> "The current thinking is that males may have some potential to recover lost germ cells after birth," says Mitchell. Longer-term xenograft studies could be designed to test that assumption in human testes, he says.

This study, combined with previous research, suggests a need for "precautionary action," says Shanna Swan, a reproductive health scientist at Icahn School of Medicine at Mount Sinai in New York, who was not involved in the study. She says it may be prudent for pregnant women to forgo the use of analgesics for minor aches and pains, though medication may be warranted for more serious conditions, such as high fever, severe pain, or migraine headaches. "Pregnant women should always consult with a physician before taking any medicine," says Swan.

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## References

1. Kristensen DM, Mazaud-Guittot S, Gaudriault P, Lesné L, Serrano T, Main KM, et al. 2016. Analgesic use—prevalence, biomonitoring and endocrine and reproductive effects. *Nat Rev Endocrinol* 12(7):381–389, PMID: [27150289](#), <https://doi.org/10.1038/nrendo.2016.55>.
2. Hurtado-Gonzalez P, Anderson RA, Macdonald J, van den Driesche S, Kilcoyne K, Jørgensen A, et al. 2018. Effects of exposure to acetaminophen and ibuprofen on fetal germ cell development in both sexes in rodent and human using multiple experimental systems. *Environ Health Perspect* 126(4):047006, PMID: [29665328](#), <https://doi.org/10.1289/EHP2307>.
3. Servey J, Chang J. 2014. Over-the-counter medications in pregnancy. *Am Fam Physician* 90(8):548–555, PMID: [25369643](#).
4. van den Driesche S, Macdonald J, Anderson RA, Johnston ZC, Chetty T, Smith LB, et al. 2015. Prolonged exposure to acetaminophen reduces testosterone production by the human fetal testis in a xenograft model. *Sci Transl Med* 7(288):288ra80, PMID: [25995226](#), <https://doi.org/10.1126/scitranslmed.aaa4097>.
5. Kristensen DM, Hass U, Lesné L, Lottrup G, Jacobsen PR, Desdoits-Lethimonier C, et al. 2011. Intrauterine exposure to mild analgesics is a risk factor for development of male reproductive disorders in human and rat. *Hum Reprod* 26(1):235–244, PMID: [21059752](#), <https://doi.org/10.1093/humrep/deq323>.
6. Lind DV, et al. 2017. Maternal use of mild analgesics during pregnancy associated with reduced anogenital distance in sons: a cohort study of 1027 mother-child pairs. *Human Reprod* 32(1):223–231, PMID: [27852690](#), <https://doi.org/10.1093/humrep/dew285>.
7. Aminoshariae A, Khan A. 2015. Acetaminophen: old drug, new issues. *J Endod* 41(5):588–593, PMID: [25732401](#), <https://doi.org/10.1016/j.joen.2015.01.024>.
8. Kugathas S, Audouze K, Ermler S, Orton F, Rosivatz E, Scholze M, et al. 2016. Effects of common pesticides on prostaglandin D<sub>2</sub> (PGD<sub>2</sub>) inhibition in SC5 mouse Sertoli cells, evidence of binding at the COX-2 active site, and implications for endocrine disruption. *Environ Health Perspect* 124(4):452–459, <https://doi.org/10.1289/ehp.1409544>.
9. Dean A, Mungall W, McKinnell C, Sharpe RM. 2013. Prostaglandins, masculinization and its disorders: effects of fetal exposure of the rat to the cyclooxygenase inhibitor indomethacin. *PLoS One* 8(5):e62556, PMID: [23671609](#), <https://doi.org/10.1371/journal.pone.0062556>.
10. Dean A, van den Driesche S, Wang Y, McKinnell C, Macpherson S, Eddie SL, et al. 2016. Analgesic exposure in pregnant rats affects fetal germ cell development with inter-generational reproductive consequences. *Sci Rep* 6:19789, PMID: [26813099](#), <https://doi.org/10.1038/srep19789>.